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Potential Complications of Influenza A Infections

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DISEASE caused by influenza A virus is usually limited to uncomplicated respiratory infection. The infection assumes major medical importance because of the potential for a large number of persons to be infected within a short period (epidemic potential) and the severe consequences of the disease in some of those infected (excess mortality). Although nonrespiratory symptoms are often as predominant as respiratory ones, the extrapulmonary manifestations are not well appreciated and, though rare by comparison with the total number of people infected, may present with regularity since epidemics may affect 50 percent of the community. The purpose of this review is to analyze the complications of influenza: (1) those responsible for causing mortality, that is, respiratory complications, and (2) extrapulmonary complications.

Pulmonary Manifestations

The usual manifestations of influenza are well known, and respiratory symptoms are predominant. Upper airway inflammation may cause obstruction leading to bacterial infection (sinusitis or otitis). Laryngitis may cause croup in children and more rarely laryngeal obstruction in older children and adults.[1,2] This complication seems related to the epidemic strain.

It is probable that *uncomplicated influenza* is regularly associated with viral invasion of the lower respiratory tract as indicated in Table 1. The evidence for this is abnormalities noted on physical examination and studies of pulmonary function, even in patients in whom no abnormalities are seen on x-ray films of the chest. Rales are heard in a variable number of patients—the most important variable apparently is the examiner.[3,4] A variety of pulmonary functions have been shown to be abnormal in uncomplicated influenza. Restrictive abnormality, as defined by a forced vital capacity (FVC) of less than 85 percent of predicted or increasing 10 percent or more with convalescence, was documented by Johanson and co-workers.[5] That these changes were due to muscular weakness or pain is possible. In this series airway obstruction was found in only one patient. However, Leeder and associates[6] found increased airway resistance in 56 percent of patients by measuring the forced expiratory flow from 25 to 75 percent of the vital capacity (FEF_{25-75}), a sensitive index of small airway changes. Johanson and co-workers also provided evidence for impaired gas exchange at the alveolar-capillary level; in six of the ten patients there was an increased alveolar-arterial oxygen tension gradient which was associated with a low arterial oxygen pressure (Po_2). In both studies when patients were restudied at six week or six months, the values either had become normal or improved. These findings were confirmed by the studies of Horner and associates[7] who showed transient decrease in the diffusion capacity. However, in the patients in this study influenza had not been confirmed, only flu-like illness during an influenza epidemic. The transience of these abnormalities had led to the conclusion that influenza is not a significant factor in causing chronic lung disease.[8]

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ABBREVIATIONS USED IN TEXT

FEF_{25-75} = forced expiratory flow from 25 to 75 percent of the vital capacity
FVC = forced vital capacity

Pneumonia is the most feared complication of influenza. Various classifications of the pulmonary manifestation have been suggested in attempt to bring order out of clinical chaos. Louria and associates[9] divided the cases of patients admitted to the New York Hospital-Cornell Medical Center during the 1957-1958 epidemic into four groups:

- Physical findings without changes on x-ray studies.
- Secondary bacterial pneumonia.
- Acute pneumonia caused by virus alone.
- Concomitant viral and bacterial pneumonia.

Hers and associates[10] arrived at a similar grouping from their pathologic studies from the same epidemic. However, in the 1968-1969 epidemic (Hong Kong virus) the clinicians at the Mayo Clinic,[11] prepared to use these concepts, were unable to make clinical distinction easily between these groups. This was especially true in cases of localized pneumonia in which cultures for bacterial pathogens and virus were both positive. They concluded that simple classification on the basis of localized versus diffuse radiographic changes allowed prognostication. It is apparent that the prognosis of pneumonia with influenza depends on the amount of pulmonary parenchyma affected. Whether diffuse pneumonia is viral alone or viral with bacterial superinfection, the prognosis is grim. In localized pneumonia there is a much better prognosis, but apparently still there is greater associated mortality than in localized pneumonia in a period without influenza activity. It is probable that localized pneumonia is usually bacterial.

TABLE 1.—*Evidence for Lower Respiratory Involvement in Uncomplicated Influenza*

Finding	*Number Affected*	*Reference*
Rales	from 4 of 76	3
	to 13 of 16	4
↓FVC	6 of 10	5
↓FEF_{25-75} (MMFR)	9 of 16	6
↓DLco	20 of 20	7

DLco = diffusing capacity of the lung for carbon monoxide
FEF_{25-75} = forced expiratory flow from 25 to 75 percent of the vital capacity
FVC = forced vital capacity
MMFR = maximal midexpiratory flow rate

Until the 1957-1958 epidemic there was little evidence that influenza virus alone could cause fatal pneumonia. The clinicopathologic studies by Louria and co-workers thoroughly established that it can. In addition they showed that this was rarely a disease of normal persons, but a disease particularly seen in the presence of rheumatic mitral stenosis.[9] Although over-interpreted as a disease unique to mitral stenosis, this relationship has been observed by subsequent investigators.[11-13] It is also clear that other chronic diseases such as chronic renal failure, as well as other forms of heart disease, are at risk. The suggested common denominator is excess pulmonary fluid.[14] Clinical observations are supported by results of animal experiments showing that sublethal doses of virus can be made lethal by instillation of fluid into the lungs.[15] Presumably, the fluid allows diffuse spread of the virus. Since persons in whom such pathophysiology cannot be evoked do die of diffuse viral pneumonia, other factors must be important. The hypothesis that some persons are uniquely susceptible or resistant to influenza virus infection on a genetic basis has received a measure of recent support.[16] This study suggests that the lower antibody response to live influenza vaccine seen in persons with HL-A type W16 (histocompatibility antigen) is due to increased cellular resistance to infection.

Of the bacteria causing pneumonia after influenza, Staphylococcus aureus has received greatest notoriety. It has been isolated from most of the fatal cases.[17] However, it is equally well known that it is not the most frequent cause of pneumonia.[9,18] In their careful study of the 1968-1969 epidemic, and its effect on admissions for pneumonia at Grady Memorial Hospital, Schwarzmann and associates[18] showed the continued predominance of the pneumococcus and important occurrence of Gram-negative bacilli as the bacteria associated with pneumonia during the epidemic. Staphylococci became more common during the epidemic, but not predominant. The data in their study, as well as in most others[9,11-14] must be interpreted with caution since the finding of a bacterial cause was based upon expectorated sputum cultures and not more definitive means of specimen collection such as transtracheal aspiration or percutaneous lung aspiration. It is also of interest that the bacteria associated with influenza epidemics seem to vary from epidemic to epidemic and from geographic area to area within an epidemic.[18]

Extrapulmonary Manifestations

The analysis of extrapulmonary influenza is difficult. When half of the population is infected in an epidemic, then concurrent illness may be accompanied by clinical and laboratory evidence for influenza. Documentation can only be accepted with reasonable certainty when (1) the virus is isolated from the pathologically affected tissue under conditions making contamination unlikely or (2) there is a concurrent rise in the incidence of the associated condition pari passu the influenza —that is, an epidemiologic association.

Isolation of influenza virus from nonrespiratory tissue has been infrequent. During the 1957-1958 pandemic, Oseasohn and co-workers and Kaji and co-workers isolated the virus from extrapulmonary tissue.[19,20] The first report of viremia was by Naficy in 1963.[21] Subsequently others have also isolated influenza from blood.[22-24] In all but one of these reports,[24] the viremia occurred either during the incubation period or during the first 48 hours of illness. In addition to culturing the virus, Oseasohn and associates also showed histopathologic alterations in a variety of tissues.[20] In short, it is proven that viremia occurs with influenza, usually during the incubation period or quite early in the course of the disease, and pathologic alterations occur in extrapulmonary tissue from which the virus also has been isolated.

Cardiovascular

Although the heart seems to be the most acknowledged extrapulmonary tissue affected by influenza, the clinical and pathologic manifestations far exceed culture documentation. Both clinical myocarditis and pericarditis have been observed. It has been suggested that influenza-associated myocarditis can take two forms: (1) *immediate,* associated with fulminating disease[20] and (2) *delayed,* occurring during late convalescence.[25] Of the 33 fatal cases studied by Oseasohn,[20] in ten there were varying degrees of acute inflammatory disease of the myocardium. Eight patients were less than 40 years old. The mononuclear infiltrate varied from perivascular to diffuse. Virus was isolated from only one, although all were appropriately cultured. Other reports have not documented myocarditis at autopsy,[9] but it is obvious that the diligence of the search is an important variable.

Pericarditis, though clinically less a problem, is somewhat better documented.[26,27] In the report of Hildebrandt and co-workers,[27] the virus was isolated from pericardial fluid in a patient with pericarditis and effusion without pneumonia. The study of Woodward and associates[27] included only cases in which there were serologic changes and isolation of the virus from the respiratory tract. Neither myocarditis nor pericarditis has been shown to occur in epidemiologic concomitance with influenza.

Neurologic

The neurologic complications are the most diverse of any organ system.[28] Encephalitis caused directly by the influenza virus can be confused temporarily with the mental aberrations of the acute febrile illness encephalopathy. Acute encephalitis appears to have an epidemiologic connection with influenza. In the 1957-1958 epidemic, in particular, an excess number of cases of encephalitis appeared in England.[29,30] In addition the virus has been isolated from the brains of patients with encephalitis,[31,32] although the possibility of contamination at time of autopsy was not excluded. An encephalopathic syndrome has occurred after influenza, but like other "postviral" encephalitis, the pathophysiology remains unknown, though immunologic mechanisms are postulated. Concurrence of encephalitis lethargica and the 1918-1919 influenza epidemic has led to speculation that the two diseases shared common causes. This was 15 years before the viral cause of influenza was shown. This association has been of greater than usual interest because of the occurrence of parkinsonism months to years later in patients who had had encephalitis lethargica. The hypothesis that parkinsonism and influenza infection are related was strengthened, but not conclusively proved by the finding of influenza A antigen discretely in the hypothalamus and midbrain of six patients with postencephalitis parkinsonism but not in patients with idiopathic parkinsonism or other neurologic illnesses.[34]

The variability in the neurologic complications seen with various influenza epidemics has been noted and tropism of selected influenza strains demonstrated.[29]

Aseptic meningitis, myelitis[36] and Landry-Guillain-Barré syndrome[37] also have been associated on occasion with influenza. The hazards of overreading the association of influenza and neurologic disease during an epidemic are illustrated by Wells.[38]

Although diffuse, severe myalgia is a conspicu-

ous manifestation of influenza, at times surpassing in frequency the respiratory manifestations. Rhabdomyolysis with myoglobinuria was not described until the 1968-1969 epidemic, and then only in a single patient with well documented influenza who had had a history of several episodes of myalgia and dark urine preceded by self-limited febrile illnesses.[39] Indeed in a subsequent report, this 27-year-old man had another episode of myoglobinuria associated with a serologically documented Coxsackie B infection.[40] In 1973, during the A-2 (London) influenza epidemic, two patients had severe rhabdomyolysis and myoglobinuria and one had acute renal failure.[41,42] Both became aware of dark urine three to four days after the onset of the influenza. Findings on muscle biopsy studies showed rhabdomyolysis but no attempts were made to isolate the virus from muscle. A similar picture of objective myositis and elevated muscle enzymes has been reported in children with both influenza A and B.[43] Reye's syndrome (encephalopathy and fatty liver) has occurred after influenza A, as it has after numerous other viral infections.[44]

Hematologic

Disseminated intravascular coagulation has been associated with influenza virus infection, as it has with numerous other infective agents.[45,46] The severity of the process in the eight cases reported was appreciable and was associated with acute renal function impairment due to fibrin deposition. Thein and co-workers[47] reported that during an epidemic of influenza in Burma, in 196 (58 percent) of 380 children admitted to the Children's Hospital because of "hemorrhagic fever" (that is, usually with vomiting, hematemesis and a positive tourniquet test) there was serologic documentation of influenza A infection. These authors properly hesitate to make a direct association because the same clinical pattern was seen with other febrile illnesses, some of which were shown to be viral and some not. They suggested that a home remedy used widely by the Burmese may be responsible.

Renal

As mentioned, renal failure during the course of influenza has been reported.[46-48] In these nine reported cases, the onset of renal symptoms or signs (oliguria or hematuria) occurred only a few days after the onset of the influenzal symptoms. In four of the patients, findings on biopsy studies showed fibrin in the renal microvasculature and in these cases disseminated intravascular coagulation (DIC) was clinically established as well. In only one of the nine was DIC not mentioned as the most likely cause of renal failure.

In 1919 Goodpasture reported the case of an 18-year-old sailor who died of glomerulonephritis and pulmonary hemorrhage six weeks after a "typical" attack of influenza.[49] A similar case but with serologic documentation of the influenza was described by Wilson and Smith.[50] The diagnosis was supported by the finding of typical linear glomerular deposits of antiglomerular basement membrane antibody by immunofluorescence. Their hypothesis was that the influenza infection may have exposed the basement membrane antigens allowing circulating antibody to react with alveoli or may have induced antibody formation. The authors offer this as "a potential lead" in the understanding of the immunopathogenesis of this syndrome.

Host Defense Mechanisms

The association between influenza infection, whether covert or manifest, and subsequent bacterial infection (usually respiratory) has been mentioned. However, the relationship between other bacterial diseases is also of interest.[51] Both influenza and meningococcal disease most often occur in the winter, usually not together. In 1971 Eickhoff and associates reported that meningococcal colonization was more than five times more common in patients with evidence of recent Hong Kong influenza than in those without. Also in the 1968 epidemic Young and co-workers[53] recounted a simultaneous outbreak of group B meningococcal disease among 55 elderly women confined to a single ward in a mental institution. In all, the cases of 48 patients were studied. Influenza was present in 24 patients and meningococcal disease in 11 (attack rate 46 percent), while in the other half meningococcal disease was found in only 4 (attack rate 17 percent). On the other hand, patients with clinical meningococcal disease were no more likely to have had influenza than were those without meningococcal disease (62.5 versus 39.4 percent). There was no correlation between systemic meningococcal infection and concurrent influenza. However, there was a correlation between serological evidence of influenza and the meningococcal strain responsible for the epidemic. They concluded that influenza

did not predispose to meningococcal disease (blood stream invasion) or increase the likelihood of airborne dissemination of the meningococcus. They did feel that the data supported the hypothesis that the virus might alter certain host factors thereby enhancing meningococcal colonization after exposure—that is, the influenza infection created a locus minoris resistentiae.

Decreased skin-test reactivity to a battery of bacterial and fungal antigens has been shown to occur during influenza infection.[54] This was observed in only the cases of seven patients in whom there was serologically documented influenza, but not in four additional persons with symptomatically similar disease but in whom there was no laboratory evidence of influenza.

Altered mononuclear phagocyte function, specifically chemotactic responsiveness, has been shown both with *in vitro* infection of the monocytes as well as those taken from naturally infected patients.[55] The mechanism for this dysfunction is unknown, but direct inaction of the monocytes by the virus is likely. Alveolar histiocytes containing influenza antigen have been observed.[10] If the alveolar macrophages and the peripheral mononuclear phagocytes are similar in response to viral infection, then the increased susceptibility to airborne bacteria is easily understood since alveolar macrophages are an important component of the pulmonary defense mechanism. In addition, impaired granulocyte chemotaxis and phagocytosis has been reported with *in vitro* infection with influenza B virus.[56] This has been confirmed with influenza A virus but not with *in vivo* influenza infection.[57]

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Orally Given Hypoglycemic Drugs and Cardiovascular Disease

I feel that we should concede that there is perhaps a relationship between the use of orally given hypoglycemic drugs and cardiovascular disease . . . If we have conceded that there is a possibility of a problem inherent in the use of the oral agents, then I think we are on poor grounds to administer orally given hypoglycemic drugs to these patients . . . There is a problem in giving these patients insulin. One has to be very careful in its administration, simply because one does not want hypoglycemia to occur in patients who are being given insulin or who are receiving any form of therapy. The reason for this is that there is an outpouring of epinephrine in these patients as a response to their hypoglycemic state and even myocardial infarction has been seen on occasion, so one must be very careful in this group of patients.

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